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Decline of antibodies in XLA infant: when to start IVIG

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Keywords: IVIG; Loss of maternal antibodies in neonates; X-linked agammaglobulinemia.

Patients with X-linked agammaglobulinemia (XLA) are protected for the first few months of life by maternal antibody, which is actively transported across the placenta during the last months of pregnancy (1). Patients do not typically present clinically with infection until after 6 months of age, when the infant's maternally derived antibody level approaches zero (2). After the diagnosis, treatment includes replacement intravenous immunoglobulin (IVIG), which significantly reduces the risk of infection (3).

Maternal antibody levels in XLA neonates may predict when to start replacement IgG.

The rate of decline for specific maternal antibody loss has not been well studied in patients with XLA that are followed from birth, even in patients with a positive family history. Information on the decline of specific maternal antibodies may be important in deciding when to start immunoglobulin replacement in these cases, apart from just knowing the serum IgG level.

We had the unusual opportunity to study specific maternal antibody decay in a full-term (39 week gestation) male infant with a BTK mutation (161delG) diagnosed prenatally with a frameshift with amino acid changes in codons 54 and 55 and a termination codon in position 56. The baby's serum IgG level was within normal limits for age at birth: 890 mg/dl (Table 1). When the child was brought to Texas Children's Hospital at 2 months of age, his IgG level had dropped to 393 mg/dl (normal), and his IgA and IgM levels were detectable. As measured at 2 months of life, the patient had serological evidence of transplacental specific maternal antibody with wide diversity to diphtheria toxoid: 0.57 IU/ml (>0.1 IU/ml protective), tetanus toxoid: 2.15 IU/ml (>0.1 IU/ml protective), *Haemophilus influenzae* type b: 1.3 μg/ml (>1.0 μg/ml protective), and 1/4 positive serotypes of pneumococcus tested in the mother 2 months postpartum (serotype 7F:4.21 μg/ml, >1.3 μg/ml protective (Table 1). Values of optimal protective levels of these antibodies were assumed from information given by the testing laboratories and clinical experience.

Lymphocyte phenotyping performed at 2 months of age confirmed the expected results: absent B cells (0.2% $CD20^+$ cells, 6 $CD20^+$ cells/μl (when compared to normal ranges 6–28%, 256–1579 cells/μl). Lymphocyte proliferation studies with mitogens and antigens were normal (data not shown).

At 3 months of age, the baby's serum IgG level dropped to 254 mg/dl (normal)

Table 1 Laboratory evaluations of B-cell function for X-linked agammaglobulinemia (XLA) carrier mother and XLA infant

	XLA carrier mother*	XLA infant†					
	2 months postpartum	Birth	2 months	3 months‡	4 months‡	5 months‡	6 months‡
Serum IgG (mg/dl)	1066	890	393	254	352	497	639
Anti-diptheria toxoid antibody (IU/μl)	0.67	ND	0.57	0.20	0.20	0.20	0.30
Anti-tetanus toxoid antibody (IU/ml)	0.78	ND	2.15	0.40	1.10	1.30	1.80
Anti-*H influenza type B antibody* (μg/ml)	>9.00	ND	1.30	0.43§	0.62§	0.93§	0.68§
Pneumococcal antibody serotype (μg/ml)							
1	1.80	ND	0.31§	0.23§	0.37§	0.67§	0.84§
7F	2.40	ND	4.21	1.47	1.39	2.18	2.08
8	2.50	ND	1.13§	0.74§	0.82§	1.16§	1.21§
19F	3.60	ND	0.60§	1.29§	1.39	1.38	1.65

*Tests performed by Quest Diagnostics, Houston, TX.
†Tests performed by LabCorp, Houston, TX.
‡IVIG 400 mg/dl at 3, 4, 5, and 6 months.
§Abnormal or nonprotective.

and his specific antibody levels decreased: diphtheria toxoid titre to 0.2 IU/ml (protective), tetanus toxoid titre to 0.4 IU/ml (protective), and *H. influenzae* type b to 0.43 μg/ml [not protective (Table 1)]. One pneumococcal serotype antibody level remained protective. IVIG replacement therapy (400mg/kg) was begun after blood for antibody titres had been obtained and was given monthly thereafter. The child responded to the IVIG infusion with progressive increases in total IgG, and many of his specific antibodies showed progressive increases in titre.

This opportunity to study serum IgG and specific antibody decline in an infant with known XLA has been instructive. That is, although serum IgG levels may be used as a surrogate marker for the infant's protection, measurements of specific antibody levels appear more sensitive. A case in point is the fall in this patient's anti-*H. influenzae* type b antibody level to a less than protective level at 3 months of age, a time in which the serum IgG level was normal. These observations are in agreement with those of other investigators who studied vertical transmission rate of several of the same antibodies in nonimmunized/nonrelevant antigen-immunized controls at birth and their persistence at 2 months of age of the infant (4, 5).

Thus, in addition to serum IgG levels in XLA infants, measurement of specific antibody levels may prove helpful in deciding when to begin IgG replacement in XLA infants.

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A case report of breastfeeding anaphylaxis: successful prophylaxis with oral antihistamines

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Keywords: anaphylaxis; breastfeeding; lactation; urticaria.

A thirty-four-year-old gravida 3 para 3 woman presented for the evaluation of recurrent cutaneous and systemic complaints associated with breastfeeding of her second and third children; there had been no problems breastfeeding her first-born. Medical history was significant for generalized urticaria with ingestion of shellfish as a teen; avoidance was practiced. There was no history of asthma or other atopy. During the initial breastfeeding attempts with her second child, ocular pruritus and erythema were noted solely with breastfeeding. On postpartum day six, generalized flushing and urticaria were noted minutes after milk letdown. Use of diphenhydramine led to imperfect control of symptoms. As feeds continued, the urticarial flares worsened. Her most severe symptoms occurred at 4 weeks postpartum during use of an electric breast pump; rapid onset of generalized pruritus and urticaria, orofacial angioedema, hoarseness and bronchospasm were noted. She was treated with parenteral diphenhydramine, solumedrol and nebulized albuterol with resolution of symptoms; serum tryptase was not obtained by emergency department staff. The patient subsequently ceased breastfeeding attempts. Two years later, a similar pattern of events occurred after the birth of her third child, with recurrence of conjunctival symptoms, flushing, urticaria, and angioedema linked temporally and exclusively with breastfeeding. There had been no interval symptoms of urticaria or angioedema.

Symptoms of breastfeeding anaphylaxis prevented with high-dose oral antihistamines.

A review of medications revealed the use of oxytocin during delivery, ibuprofen, docusate sodium, iron and multivitamins; all were stopped without cessation of symptoms. Evaluation for potential allergic or other aetiologies failed to identify the aetiology. Physical examination was normal. Total IgE was normal. A 50-antigen aeroallergen RAST (ImmunoCAP Pharmacia Diagnostics, Uppsala, Sweden) panel and a 4-antigen shellfish RAST panel were negative, as was prick testing for shrimp. Breastfeeding anaphylaxis (BFA) was diagnosed. As the patient refused avoidance, cetirizine 10 mg twice daily was initiated. As part of her ongoing workup, a baseline serum tryptase was desired, but she declined given complete control of symptoms on this new regimen. She continued breastfeeding without difficulty.